DESIGN, FORMULATION AND EVALUATION OF TOPICAL FORMULATION FOR MEFENAMIC ACID- A NOVEL NANOCARRIER APPROACH IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Synopsis submitted to the IIMT University in partial fulfillment of the requirements for the award of the Degree of

DOCTOR OF PHILOSOPHY

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By

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INTRODUCTION

Rheumatoid Arthritis

Rheumatoid arthritis or RA is an autoimmune and inflammatory disease in which the immune system mistakenly attacks healthy cells in the body, causing inflammation (painful swelling) in the affected body part.

RA mainly affects joints, usually several joints at once. RA generally affects joints in the hands, wrists, and knees. In joints with RA, the lining of the joint becomes inflamed and damages the joint tissue. This tissue damage can cause long-term or chronic pain, instability (lack of balance), and deformities (deformities).

RA also affects other tissues throughout the body and can cause problems with organs such as the lungs, heart, and eyes.

Topical Drug Delivery Systems6

Topical drug delivery systems are drug delivery methods applied to specific parts of the body, usually the skin, to treat a variety of conditions. There are many common forms of topical medications such as lotions, gels, patches, and powders, but most are available as creams or ointments.

Etosome2

Etosome is a non-invasive vehicle that allows the penetration of drugs deep into the skin and/or into the systemic circulation. Ethosomes represent a novel alternative drug delivery system and are currently the focus of many studies. Etosomes are soft, flexible vesicles composed primarily of phospholipids, ethanol, and water.

- **Transosome1**

Transosomes are a type of elastic or deformable vesicle, first introduced in the early 1990s. Elasticity is provided by including edge activators in the structure of the lipid bilayer.

The original composition of these vesicles was soya phosphatidyl choline integrate sodium cholate and a small concentration of ethanol. Transfersomes are applied in a non-occluded method to the skin and have been shown to penetrate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. For a lot of molecules, peptides, vaccines and proteins, they serve as drug carriers. Their drug carrier ability is in vitro and in vivo as well.

- **Liposomes3**

A liposome is a spherical-shaped vesicle that is composed of one or more phospholipid bilayers, which closely similarity the structure of cell membranes. Their usage as drug delivery systems stems from the fact that they can encapsulate hydrophilic or lipophilic drugs.

- **Mefenamic acid5**

Mefenamic acid' or 2-(2, 3-dimethylphenyl) amino-benzoic acid belongs to non-steroidal anti-inflammatory drugs (NSAIDS) therapeutic class. It is used in treating acute to moderate pain such as headache, fever, dysmenorrheal ache, osteo-arthritis, rheumatoid arthritis and swelling

[1]. This drug is categorized in class II according to the Bio-pharmaceutical classification system (BCS) which has lower water solubility but higher permeability [2].

Anti-inflammatory analgesic like mefenamic acid are also called non-steroidal anti-inflammatory drugs (NSAIDs), or sometimes just 'anti-inflammatories'. Mefenamic acid is used to treat painful conditions such as arthritis, pain assistant with heavy menstrual bleeding, and pain after surgical operations.
Mefenamic acid works by blocking the action of a natural chemical called the cyclooxygenase (COX) enzyme. These enzymes help the body produce other chemicals called prostaglandins. Some prostaglandins are produced at or at the site of injury and cause pain and inflammation. By blocking the action of the COX enzyme, fewer prostaglandins are produced, reducing pain and inflammation.

1. OBJECTIVE OF WORK INCLUDING SCOPE OF STUDY AND HYPOTHESIS

Transdermal delivery is attractive due to availability. However, drug delivery through the skin remains a challenge in biomedicine. Over the past few decades, a variety of successful new devices and methods have emerged to optimize drug delivery across the skin, and their hindrances limit the penetration of most therapeutics. Failure of various conventional antifoam formulations, such as: liposomes to pass through the tapered (>30 nm) intercellular channels of stratum corneum, rendered invention of some lipid based vesicular carrier systems such as ethosomes which consist of phospholipid, ethanol and water. Ethosomes can provide better skin permeation than liposomes and deliver enhanced amounts of both small and large therapeutic agents through skin and targeting to deeper skin layers for various diseases. Finally deliver to the systemic circulation. Due to the presence of ethanol, ethasomal carrier cause skin disruption as well as lipid fluidity is increased.

Ethosomes are relatively new vesicular carriers composed mainly of phospholipids, ethanol and water. The absorbing features of ethosomes are due to their high ethanol content which facilitates their penetration through stratum corneum and target intensely skin layers [2,24]. This is advantageous compared with conventional liposomes which have narrow penetration through the skin and remain constricted in the upper layer of the stratum corneum [25]. Compared to liposomes, ethosomes had greater holding capacity of methotrexate into the skin for a longer period of time, suggesting a better therapeutic outcome [26].
It was shown that the quantity of tacrolimus leftover in the epidermis at the end of a 24-h experiment was significantly greater from the ethosomes than from commercial ointment. Further, in- vivo topical application of ethosomal tacrolimus expose efficient suppression of the hypersensitivity compared to traditional liposomes and commercial ointment [27].

Jang et al. showed that the transdermal flux and skin deposition of psoralen-loaded ethosomes were 3.5 and 2.15 times higher than those of liposomes, respectively [28]. We also showed that ethosomes had approximately 6-fold higher penetration of voriconazole through rat abdominal skin compared to an aqueous-alcohol solution of the drug [29].

Encapsulating drugs in transfersomes is one potential approach to address this issue. It has a bilayer structure that facilitates the encapsulation of lipophilic and hydrophilic drugs as well as amphiphilic drugs with higher permeation efficiency compared to conventional liposomes. Transfersomes are elastic in nature and can be deformed and squeezed like intact bubbles through narrow pores much smaller than their size.

Liposomes are predominantly used as a drug delivery vehicle to administer nutrients such as lipid nanoparticles in mRNA vaccines and DNA vaccines. Liposomes are most commonly possessed of phospholipids, particularly phosphatidylcholine, but may also contain other lipids, such as egg phosphatidylethanolamine, provided they are compatible with the structure of the lipid bilayer. Liposomal structures can adhere to unhealthy tissues using surface ligands.

Hypothesis-

Mefenamic acid is a nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs is used as analgesic,anti-inflammatory,and to reduce fever

It is unconfirmed the way it decreases pain. It might reduce swelling by lowering levels of prostaglandin. It is used to treat mild to moderate pain of RA and dysmenorrhea (menstrual cramps).

Pain in rheumatoid arthritis is but one of the symptoms. There is also a psychological or spiritual illness and a deep depression, with feelings of hopelessness and anxiety in seeing no future and feeling thwarted, of incapability to work or play.

In light of the above, the aim of the present study is to design, formulation and evaluation of topical formulation for mefenamic acid- novel nanocarrier approach in the treatment of rheumatoid arthritis

2. Literature Review

- Baboota et al.,(2006) prepared and evaluated transdermal gels of diclofenacdiethylamine by using penetration enhances such as olesan oil and dimethyl sulfoxide and using different polymers such as carbopol-940, polyvinyl alcohol, hydroxy propyl methyl cellulose-k(4)M, hydroxy propyl cellulose-M, and sodium carboxy methyl cellulose. Selected formulation were evaluated for their anti-inflammatory activity using the carrageenan-induced paw edema in rats.. In vivo study for the selected formulation showed a sustained reduction in inflammation in the carrageenan induced paw edema in rats. The efficacies of carbopol-940 and PVA gels were also compared with that of the marketed Vovera gel, (R) and it was found that carbopol and PVA gels produced better results than the Voveran gel(c) 2006 Prous Science .All rights reserved.

- Babu,R.J; et al (2009),Transdermal administration of Phenylbutazone (PBZ) would be beneficial in large animals in terms of minimizing gastro-intestinal ulcerations and other side effects, easy administration to legs and joints and minimizing the dose to reduce systemic toxicity of the drug. By increasing drug loading from 1% to 5% w/w, the steady-state flux (microg/cm(2)/h) of PBZ was increased two fold (P0.001). Similarly, by increasing the MSA concentration from 0% to 4 the steady- state flux (microg/cm(2)h) of PBZ was increased to fold (P0.001). Overall, by increasing the drug load and the use of an approriate amount of the penetration enhancer, the steady-state flux of PBZ through skin was increased four fold(P0.001). MSA at both 2% and 4% w/w concentration significantly increased the skin levels of PBZ as compared with control (P 0.05). Hence, MSA served as an effective skin- penetration enhancer in the liposomal gel of PBZ for deer.

- Banks,S.L; et al (2011), Animals treated with microneedles+Solaraze® displayed extended pore lifetime (determined by transepidermal water loss measurements) for up to 7 days. Enhanced naltrexone permeation was also observed for an extended amount of time in animals trated with microneedles+Solaraze®. None-specific COX inhibition is an effective means of extending pore lifetime following microneedle treatment in hairless guinea pigs.

- Berlin,J.M; et al(2008), These subjects were randomizid into 2 arms of the study: cryosurgery alone and cryosurgery followed by diclofenac sodium 3% gel for a period of 90 days. Lesion counts were assessed at baseline, and 45,75,105 and 135 days after cryosurgery.Of the 521 patients enrolled in the study who successfully completed all of the visits concluding on day 135,277 were in the cryosurgery alone arm and 244 were in the cryosurgery followed by diclofenac sodium 3% gel arm.

- Campione,E;et al (2010), to evaluated the efficacy and tolerability of piroxicam 1% gel in the treatment of actinic keratoses. Piroxicam 1% gel was applied twice daily for 12 weeks to 31actinic keratoses.The lesions were evaluated clinically and by means of dermoscopy at an initial baseline visit,at intermediate visits,and after 90 days.

- Dow,G et al(2006), Rosacea is a common chronic dermatosis that often is characterized by the presence of facial erythema, visible blood vessels,papules and pustules. Because the face is the predominant site of involvement, rosacea may cause serious psychologic trauma and can significantly affect the quality of life of individuals with the condition.A stable aqueous gel formulation of 1% metronidazole has been devloped by the novel combination of hydrosolubilizing agents. Metronidazole 1% gel is clear gel that exhibits advantageous qualities. Data are presented from a 21-day cumlative irritation study,an assessment of skin barrier function,an in vitro skin penetration study,an absorption following maximal topical exposure study,and a skin hydration study.

- Dubey et al (2009), Transdermal gel formulatoin of ketorolac tromethamine (ketorolac) for the treatment of nociceptive somatic pain.The formulation was optimized for skin permeation enhancers, pH of the system,and dosage strength using in vitro and in vivo techniques. Of the various permation enhancers evaluated, dimethyl sulfoxide (DMSO) and oleic acid were found to singnificantly increase skin permeation flux of ketorolac. Tha concentration of DMSO affected the rate as well as exxtent of transdermal absorption.

- Gou,M et al (2009), Rapid local transdermal anaesthetic is desirable in clinic. In this paper, lidocaine loaded poly(epsilon-caprolactone)-poly(ethylene glycol)-poly(epsilon-caprolactone) (PCL-PEG-PCL).Nanoparticles were prepared, and a novel transdermal lidocaine formulation:lidocaine loaded PCL-PEG-PCL nanoparticles in F127 hydrogel (Nano-Lido Gel),was demonstrated.These lidocaine loaded PCL-PEG-PCL nanoparticles with mean particles size of ca. 200 nm had drug loading of about 40 the efficiency of transdermal anaesthesia of four ultrasound pretreatment (NU), was evaluated by tail-flick latency test assay in rats.

- He,W; et al(2008), Transdermal permeation enhancenment of N-trimethyl chitosan (TMC) with different degrees of quaternization(DQ). Testosterone (TS) used as an effective drug, four different gels were prepared without enhancer, with 5% TMC40%,5%TMC 60or 2% Azone, respectively as enhancer. Compared to the TS gel without enhancer, TS gels with enhancers all showed significant enhancing effect on transdermal permeation of TS(P0.05). Meanwhile, compared to 2%. Azone, 5% TMC60 had a stronger enhancement (P0.05) while 5% TMC40 had a similar effect(P>0.05). The results suggested that the enhancement of TMCs increased with the increase of DQ.

- Hikima,T;et al (2009), The mechanism of skin penetration enhancement by ultrasound under sonophoresis (US) or by an electrical field under iontophoresis (IP) was investigated using hairless mouse skin in vitro. Donor gel with the chemicals was loaded on the skin surface and then the skin was treated with US (300kHz,5.2W/cm(2), 5.4%

(duty-cycle) and IP (0.32+/-0.03 mA/cm(2) individually or with US and IP in combination (US+IP). The profiles of ionized chemicals for US+IP were the same as profile for IP, while the penetration flux of a non-ionized chemical synergistically increased with US+IP composed with the individual flux of US and IP . The chemicals with molecular weight of more than 1000 showed synergistic effects with US+IP. Therefore the synergistic effects of US+IP was mainly caused by the SC diffusivity of chemicals increased by US and the electroosmotic water flow by IP application.

- Krishnainh,Y.S. et al (2008c), The in vitro transdermal permeation of trimetazidine permeation of trimetazidine from hydroxypropylmethyl cellulose (HPMC) gel drug reservoir system using nerodilol, There was an increase in the amount of trimetazidine (8,719.7+/-153.3 microg/cm(2)) permeated across the rat epidermis up to 24 h(Q(24)) with an increase in nerodilol concentration (5%w/v) in HPMC gel drug reservoir. However , no significant difference ($p>0.05$) was observed in the amount of drug permeated (Q(24)) with 5% w/v of nerodilol when compared to that obtained with 4% w/v of nerodilol (8,484.5+/-165.8 microg/cm(2zidine)). The HPMC gel drug reservoir containing 4% w/v of nerodilol showed optimal transdermal permeation of trimezidine.

- Lopes,L.B et al (2007), The lipid formulation used in this study contains monoolein(MO),The skin penetration of vit-K was assessed in vitro using porcine ear skin mounted in a Franz diffusion cell. Vit K(2.5 w/w) was incorporated in either of three formulations: The hexagonal phase gel and the nanodispersion delivered approximately 2 times more vitK to the SC and 2.0-3.7 times more vitK to the (E+D) than the vaseline solution. These results demonstrate that the topical delivery of vit K incorporated in a lipophilic vehicle is small, but it may be enhanced by MO-based system, which might be useful to increase the effectiveness of topical vitK therapy. The skin flux of bupivacaine solution through rabbit ear skin was 105± 24_g/cm2/h, the effective permeability coefficient was 26×10-3+-9× 10-3 cm/h,and 77± 15% of bupivacaine was permeated. Bupivacaine-loaded gels allow the drug was permeated through the skin.47±4% and 36±3% of the drug amount included in 75A/25MMI and 60A/40MMI hydrogels respectively, was permeated.The skin flux of the drug was between 90±5and 16±7g/cm2/h depending on the amount of bupivacaine included in the gel and the gel composition. Furthermore, as more MMI in the gel slower skin flux of the drug due tobupivacaine-geL.

- Mehta M. et al., (2014)explained ethosomes- a noninvasive approach for transdermal drug delivery systems that showed tansdermal drug delivery system was useful for topical and local action of the drug.

- Preeti et al., (2014) developed of Celecoxib ethosomes gel for the treatment of Rheumatoid Arthritis. Results showedthat transferosomal gel of Celecoxib possessed better skin permeation potential, better stability and higher entrapment efficiency, easy to scale up and ability as a self penetration enhancer.

- Honggeng G. et al., (2014) developed Curcumin attenuated acute Propioni bacterium acnes-induced through inhibition of HMGB1 expression in mice. resulted that found massive hepatocyte apoptosis pericentral areas 7 days after P. acnes priming curcumin treatment reduced hepatocyte apoptosis significantly.

- Abdullah R. et al., (2013)studied on ethosomes as a transdermal drug delivery system for enhancement the antifungal activity of nystatin,which showed transferosomes as a transdermal drug delivery system for enhancement the antifungal activity of nystatin. It can be developed successfully to improve the antifungal activity.

- Sureewan D. et al., (2013) developed of Meloxicam-Loaded Cationic ethosomes as Transdermal Drug Delivery Carriers describes thata penetration-enhancing mechanism of transferosomes, such as the vesicle adsorption to and or fusion with the SC, was observed. This study suggests that cationic transferosomes have the potential to be dermal delivery carriers of MX.

- Prajapati T. S. et al., (2011)developed ethosomes: A Vesicular Carrier System for transdermal drug delivery resulting thus ultra deformable vesicles can provide the novel solution for the transport related problems. They are free from the rigid natureof conventional vesicles and can transport even the large molecules. They work on number of mechanisms working together to provide an excellent carrier system for the drug transport.

- Shailesh T. et al., (2011) explained that the ethosomes is an ultra-deformable vesicle, thus has the property which can squeeze itself through a pore which is many times smaller than its size owing to its elasticity. These drugs find place in different places in the elastic vesicle before they get delivered beneath the skin. Peripheral drug targeting, transdermal immunization can also be achieved with this type of drug delivery system.

- Walve J. et al., (2011) discussed that the transdermal route of drug delivery. Which resulting among these ethosomes can act as a carrier for low as well as high molecular weight

- Gavali M. etal., (2011)explaineda novel vesicular drug carrier system called ethosomes, which is composed of phospholipid, surfactant, and water for enhanced transdermal delivery and the transfersomal system was much more efficient.

- Narayana S. et al., (2011)discussed the vesicular drug carrier systems ethosomes (ultra-deformable carrier systems) are novel carriers, which are composed of phospholipid, surfactant, and water which enhanced the transdermal drug delivery systems (TDDS).This high deformability gives better penetration of intact vesicles, and transfersomes arehighly flexibility of particles, so drug targeting can be achieved by this type of delivery systems.

- Butoescu A. et al., (2009) developed Intra-articular drug delivery systems for the treatment of rheumatic diseases which showed the research on encapsulation techniques should take into account specific targeting strategies for cellular receptors in the joint, which could represent a major breakthrough in the domain of rheumatic disease treatment.

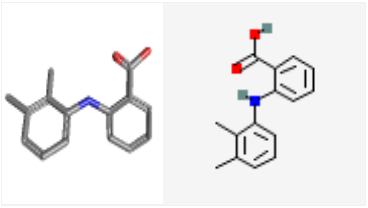
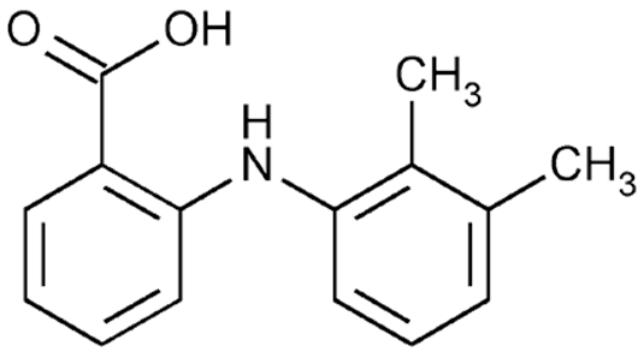
- Pandey S. et al., (2009)discussed ethosomes: a novel Approach for transdermal drug delivery which showedsuch as highly deformable particles can thus be used to bring drugs across the biological permeability barriers, such as skin. When tested in artificial systems

- Ceve G. et al., (2003) developed biological activity and characteristics of triamcinolone-acetonide formulated with the self-regulating drug carriers, ethosomes.Whichobserved that the owing to their widespread use, corticosteroids have been incorporated into many modern drug delivery systems.

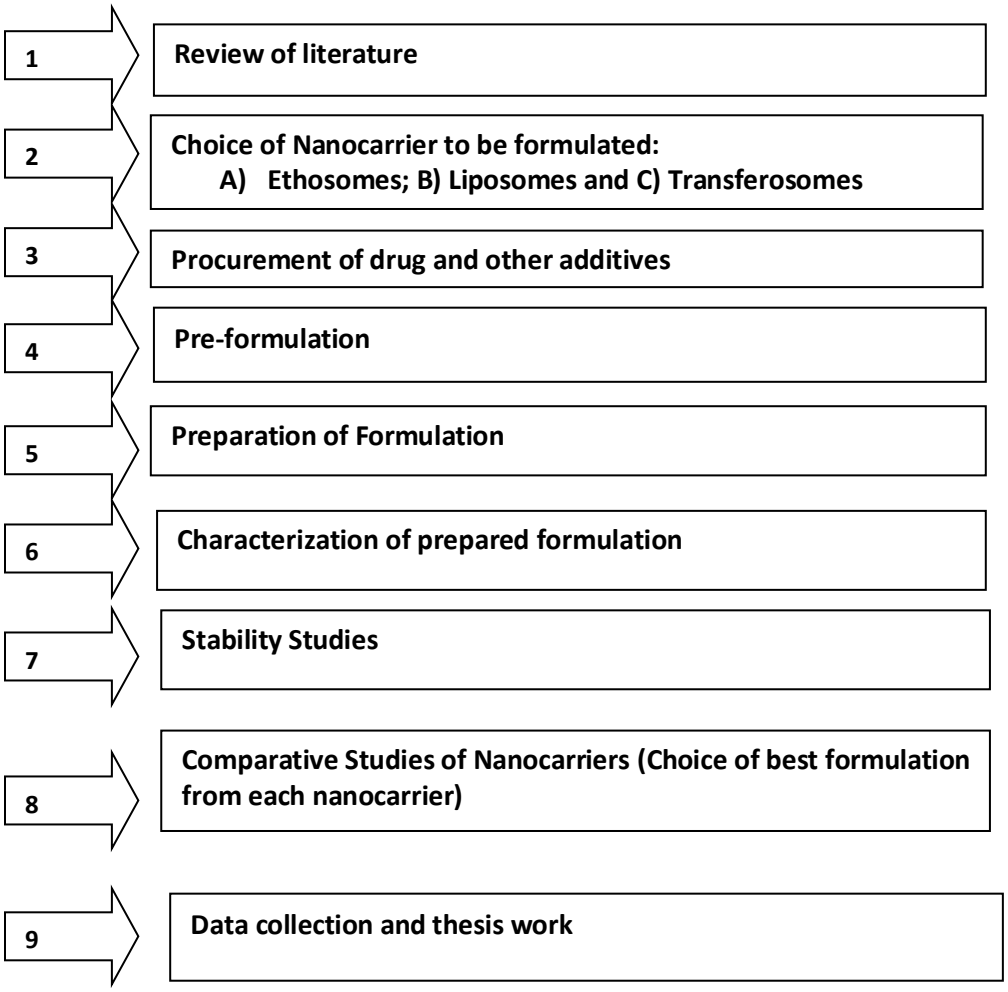
- Shah C. J. et al., (2001) developed Cubic phase gels as drug delivery systems that shownone of the ways to circumvent this problem has been the use of considerably less viscous lamella r phase gel, convert to the cubic phase.

- GavaliM.S. et al., explained Clinical p erythroosome: a new technique for transdermal drug delivery showed that drug laden erythrosomes can carry unprecedented amount of drug per unit time across the skin (up to 100mg cm2h-1).

3. Drug Profile:

Structure	 3D 2D 
Molecular Formula	C15H15NO2
Molecular Weight	241.28
Chemical Name	2-[(2,3-dimethylphenyl)amino]benzoic acid

4. Plan of Work



5. Methodology

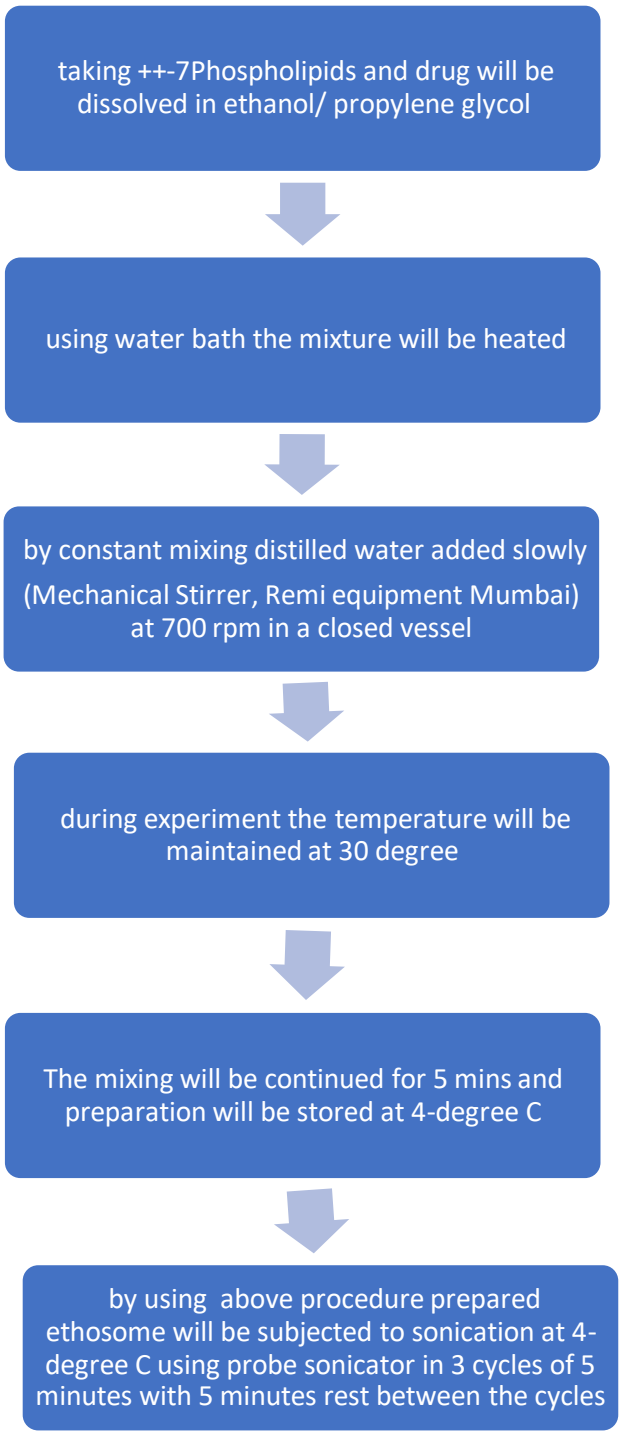
A) Preparation of Ethosomes-

» Pre-formulation studies of drug, polymers and other ingredients:
The following tests will be performed for pre-formulation studies.
a. Identification of selected drugs: It will be confirmed by various analytical techniques like UV, FTIR spectroscopy and DSC.
b. Melting point: Melting point of the drug sample will be determined by using capillary melt method.
c. Solubility studies: Standard method for solubility determination will be used.
d. Partition coefficient: By shake flask method

» Preparation of calibration drug: Suitable analytical method will be developed for selected drugs using UV spectrophotometer.

» Physiochemical characterization of drug and polymers and their compatibility study-
1. Differential scanning calorimetry (DSC) study.
2. Attenuated total reflection- fourier transform infrared spectroscopy (ATR-FTIR) study.

» Preparation and optimization of ethosomes-


taking ++-7Phospholipids and drug will be dissolved in ethanol/ propylene glycol
using water bath the mixture will be heated
by constant mixing distilled water added slowly
(Mechanical Stirrer, Remi equipment Mumbai) at 700 rpm in a closed vessel
during experiment the temperature will be maintained at 30 degree
The mixing will be continued for 5 mins and preparation will be stored at 4-degree C
by using above procedure prepared ethosome will be subjected to sonication at 4-degree C using probe sonicator in 3 cycles of 5 minutes with 5 minutes rest between the cycles

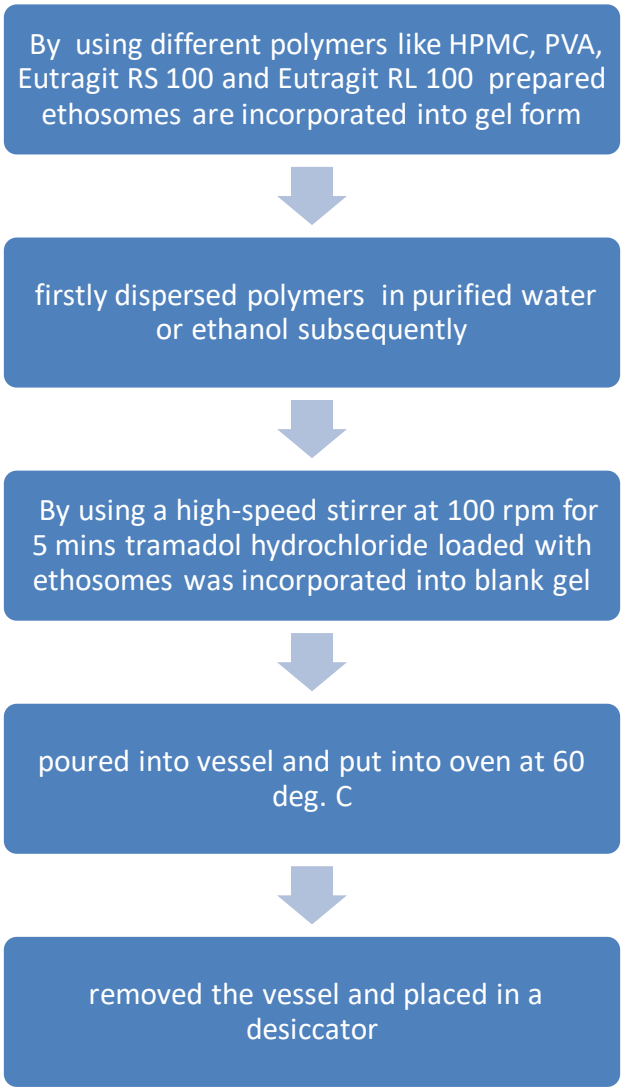
● By using ethanol injection method ethosomes will be prepared and parameters of optimization are as follow:

- ✓ Ratio of surfactant/lipid
- ✓ Effects of charge-inducing agent
- ✓ Rotation speed of magnetic stirrer

» Characterization of optimized ethosomes

- ✓ Vesicle size, Polydispersity Index and Zeta Potential
- ✓ Vesicle shape
- ✓ TEM
- ✓ Surface morphology and internal structure (Electron Microscopy) (SEM)
- ✓ AFM
- ✓ Entrapment efficiency
- ✓ In-vitro drug release studies

» Preparation of ethosomal gel-


By using different polymers like HPMC, PVA, Eutragit RS 100 and Eutragit RL 100 prepared ethosomes are incorporated into gel form
firstly dispersed polymers in purified water or ethanol subsequently
By using a high-speed stirrer at 100 rpm for 5 mins tramadol hydrochloride loaded with ethosomes was incorporated into blank gel
poured into vessel and put into oven at 60 deg. C
removed the vessel and placed in a desiccator

● Prepared ethosomal suspension will be incorporated into the HPMC, PVA, eudragit RS 100 and eudragit RL 100 gel.

» Characterization of ethosomal gel-

- ✓ Following evaluation parameters will be performed for the ethosomal gel-
- ✓ Optical Microscopic Observation
- ✓ pH measurement
- ✓ Thickness
- ✓ Folding endurance
- ✓ Moisture content
- ✓ Determination of drug content
- ✓ In-vitro drug release studies
- ✓ Stability studies

» In- vivo study-

In vivo antihypertensive activity of transdermal patch in albino rats for the treatment of hypertension will be performed by following test-

- ✓ Conditioning / training of animals
- ✓ Measurement of Initial Blood Pressure of Rats
- ✓ Induction of hypertensive in normotensive rats
- ✓ Post –TDDS treatment Blood Pressure Assessment of MPA-induced hypertensive rats

B) Preparation of Liposomes

» Pre-formulation studies of drug, polymers and other ingredients:

The following tests will be performed for pre-formulation studies.

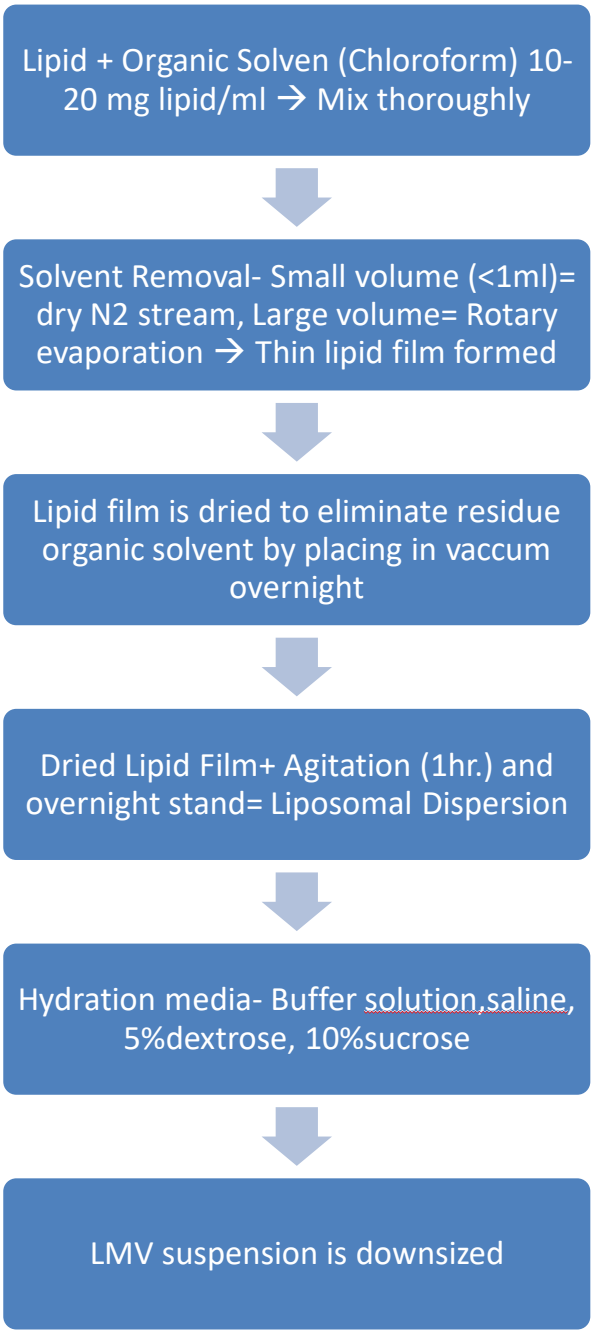
a. Identification of selected drugs: It will be confirmed by various analytical techniques like UV, FTIR spectroscopy and DSC.

b. Melting point: Melting point of the drug sample will be determined by using capillary melt method.

c. Solubility studies: Standard method for solubility determination will be used.

d. Partition coefficient: By shake flask method

» Preparation and optimization of liposomes-


Lipid + Organic Solven (Chloroform) 10-20 mg lipid/ml → Mix thoroughly
Solvent Removal- Small volume (<1ml)= dry N2 stream, Large volume= Rotary evaporation → Thin lipid film formed
Lipid film is dried to eliminate residue organic solvent by placing in vaccum overnight
Dried Lipid Film+ Agitation (1hr.) and overnight stand= Liposomal Dispersion
Hydration media- Buffer solution,saline, 5%dextrose, 10%sucrose
LMV suspension is downsized

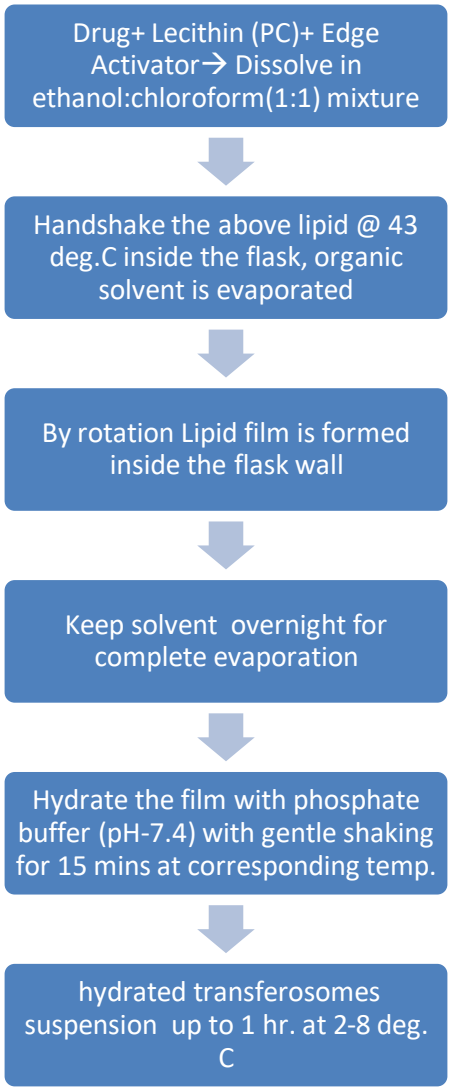
» Evaluating parameters of liposomes-

C) Preparation of Transferosomes

» Pre-formulation studies of drug, polymers and other ingredients:
The following tests will be performed for pre-formulation studies.
a. Identification of selected drugs: It will be confirmed by various analytical techniques like UV, FTIR spectroscopy and DSC.
b. Melting point: Melting point of the drug sample will be determined by using capillary melt method.
c. Solubility studies: Standard method for solubility determination will be used.
d. Partition coefficient: By shake flask method

» Preparation of calibration drug: Suitable analytical method will be developed for selected drugs using UV spectrophotometer.

» Preparation and optimization of transferosomes-


Drug+ Lecithin (PC)+ Edge Activator→ Dissolve in ethanol:chloroform(1:1) mixture
Handshake the above lipid @ 43 deg.C inside the flask, organic solvent is evaporated
By rotation Lipid film is formed inside the flask wall
Keep solvent overnight for complete evaporation
Hydrate the film with phosphate buffer (pH-7.4) with gentle shaking for 15 mins at corresponding temp.
hydrated transferosomes suspension up to 1 hr. at 2-8 deg. C

» Evaluating parameters of transferosomes -

» Thesis Writing and Computation of data

7. CONCLUSION

The novel mefenamic acid ethosomal gel may be appeared to be effective in the management of rheumatoid arthritis and related inflammatory conditions. It may be effective in getting relief from pain of rheumatoid arthritis.

Since there was no nanocarrier formulations available in market and used before, however nanocarrier formulation this will show improvement in spontaneous pain, morning stiffness, pressure tolerance, swelling, mobility and muscle power. No significant improvement was observed in ESR or other biological parameters.

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